

# A Computational Model-Based Validation of Guyton's Analysis of Cardiac Output and Venous Return Curves

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## Abstract

*Guyton developed a popular approach for understanding the factors responsible for cardiac output (CO) regulation in which 1) the heart-lung unit and systemic circulation are independently characterized via CO and venous return (VR) curves, and 2) average CO and right atrial pressure (RAP) of the intact circulation are predicted by graphically intersecting the curves. However, this approach is virtually impossible to verify experimentally. We theoretically evaluated the approach with respect to a nonlinear, computational model of the pulsatile heart and circulation. We developed two sets of open circulation models to generate CO and VR curves, differing by the manner in which average RAP was varied. One set applied constant RAPs, while the other set applied pulsatile RAPs. Accurate prediction of intact, average CO and RAP was achieved only by intersecting the CO and VR curves generated with pulsatile RAPs because of the pulsatility and nonlinearity (e.g., systemic venous collapse) of the intact model. The CO and VR curves generated with pulsatile RAPs were also practically independent. This theoretical study therefore supports the validity of Guyton's graphical analysis.*

## 1. Introduction

Cardiac output (CO) curves characterize the ability of the heart-lung unit to pump oxygenated blood to the systemic circulation, while venous return (VR) curves represent the ability of the systemic circulation to return deoxygenated blood back to the heart-lung unit. Since CO and VR curves each depict average flow rate as a function of average right atrial pressure (RAP) and CO must equal VR in the steady-state, Guyton stated that one could, in principle, predict average CO as well as average RAP in the intact circulation by measuring each of these curves (while preserving the hemodynamic state) and then graphically establishing their intersection [1]. The important implication of this graphical analysis is that the heart-lung unit and systemic circulation may be considered independently. That is, a change in the state of the heart-lung unit due to, for example, a change in heart rate will only alter the CO curve, while a change in the state of the systemic circulation due to, for

example, a change in total peripheral resistance will only vary the VR curve. Thus, Guyton's analysis of CO and VR curves has been frequently utilized to understand the factors responsible for CO regulation.

To measure experimentally CO and VR curves, Guyton and others [1] developed sophisticated open circulatory preparations in which RAP could be set to arbitrary constant values. Consequently, these experimental preparations permitted one curve to be determined independently of the other, which is consistent with the implementation of Guyton's graphical analysis. However, the correspondence between average CO and RAP determined by the intersection of experimental CO and VR curves and average CO and RAP measured directly from the intact circulation has not been previously demonstrated. The reason is that it is virtually impossible to measure both CO and VR curves as well as intact, average CO and RAP in a single animal while precisely maintaining the hemodynamic state. In fact, Guyton concluded that he could not match any point on his experimentally determined VR curve with the intact circulatory values obtained from the same animal because the circulatory state could not be preserved [2].

Theoretically, even if the hemodynamic state could be held perfectly constant, the intersection of CO and VR curves obtained with experimental preparations which apply constant RAPs may not be able to predict accurately intact circulatory values due to the pulsatility and nonlinearity (e.g., systemic venous collapse) of the heart and circulation. Indeed, Guyton demonstrated that pulsatility could substantially alter the VR curve by developing an experimental preparation in which RAP could be set to sinusoids of varying amplitude [3].

In this paper, we investigate the ability of Guyton's graphical analysis to predict intact circulatory values. Our study is based on a computational model of the heart and circulation, because, in contrast to an animal study, the hemodynamic state can be exactly controlled. We specifically apply the graphical analysis to two sets of model CO and VR curves which are obtained by simulating established experimental preparations that apply constant RAPs and implementing theoretical preparations that apply pulsatile RAPs similar to those seen in the intact circulatory model.

## 2. Model of the heart and circulation

We constructed a lumped parameter model of the human pulsatile heart and circulation that is capable of generating the hemodynamic behaviors required by this study, namely pulsatile waveforms and CO and VR curves. The model is illustrated in Figure 1 in terms of its electrical circuit analog in which charge is analogous to blood volume, current, to blood flow rate ( $\dot{q}$ ), and voltage, to pressure ( $P$ ). The model consists of six compartments which represent the left and right ventricles ( $l, r$ ), systemic arteries and veins ( $a, v$ ), and pulmonary arteries and veins ( $pa, pv$ ). Each compartment consists of a conduit for viscous blood flow with resistance ( $R$ ) and a volume storage element with compliance ( $C$ ) and unstressed volume. Two of the resistances and two of the compliances are nonlinear (denoted with boxes). The systemic venous resistance is represented by a Starling resistor (with chamber pressure set to atmospheric pressure), while the pulmonary arterial resistance is represented by an infinite number of parallel Starling resistors (with chamber pressure equal to alveolar pressure), arranged vertically, one on top of the other. The pressure-volume relationships of the left and right ventricles consist of an essentially linear regime, a diastolic volume limit, and a systolic pressure limit. The compliances of the linear regime vary periodically over time and are responsible for driving the flow of blood. The four ideal diodes represent the ventricular inflow and outflow valves and ensure uni-directional blood flow. The reference pressure is set to thoracic ( $th$ ) pressure for the ventricular and pulmonary compartments.

Although atria are not explicitly included in the model,  $P_{ra}^*(t)$  represents the model's effective "right atrial" pressure (ERAP). Important to this study, the mean value and peak-to-peak amplitude of this pressure compares favorably with average human RAP. Moreover, the effects of atria on diastolic filling are accounted for by adjusting the parameter values of adjacent elements. See [4] for parameter values and additional model details.

## 3. Measuring venous return curves

Figure 2 illustrates the two open circulatory models for measuring VR curves that we implemented. Since the mean systemic pressure must be held exactly constant when measuring VR curves, each model includes an independent current source ( $\dot{q}_v(t)$ ) which pumps into the systemic circulation whatever is pumped out. The model of Figure 2a mimics an established experimental preparation in which constant ERAP is applied and varied with a voltage source, while the model of Figure 2b is a theoretical preparation in which pulsatile ERAP similar to that seen in the intact circulatory model is applied. The VR curve for the latter model may be obtained by adjusting the value of the right

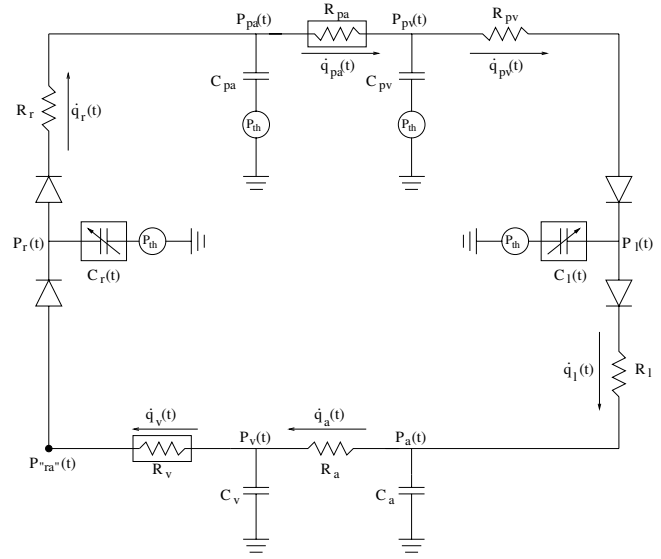


Figure 1. Model of intact pulsatile heart and circulation.

ventricular diastolic compliance in order to vary average  $P_{ra}^*(t)$  and measuring the average  $\dot{q}_v(t)$ . Importantly, since this model includes heart-lung unit parameters (*e.g.*, heart rate), the VR curve may be sensitive to these parameters. That is, the VR curve may be dependent on the CO curve which would limit the utility of Guyton's analysis when applied to VR curves measured in this manner.

The VR curves generated from both of these models account for the major physiology reflected by the corresponding experimentally measured curves. These model curves are quantitatively identical at high ERAPs, because the Starling systemic venous resistance looks like a linear resistance at these pressures. However, the model curves are significantly different for RAPs near atmospheric pressure, since the Starling systemic venous resistance behaves nonlinearly at these pressures.

## 4. Measuring cardiac output curves

Figure 3 illustrates the two open circulatory models for measuring CO curves that we implemented. The model of Figure 3a specifically mimics an established experimental preparation in which constant ERAP as well as arterial pressure are applied with voltage sources. The model of Figure 3b is a theoretical preparation in which pulsatile ERAP similar to that seen in the intact circulatory model is applied. The CO curves for each of these models may be obtained by simply varying  $P_{ra}^*$  or  $P_v$  and measuring the average  $\dot{q}_l(t)$ . Note that the latter model includes the systemic venous resistance which partly determines the VR curve. However, since this parameter is usually constant, its

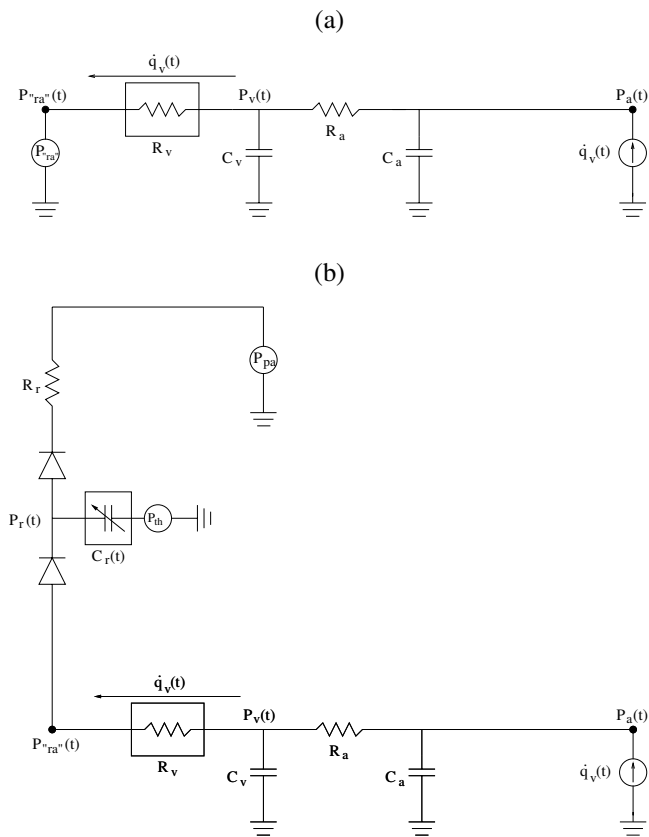


Figure 2. Models for measuring VR curves.

effect on the measured CO curve is inconsequential. Thus, the CO curve is practically independent of the VR curve.

The CO curves generated from both of these models also account for the major physiology reflected by the corresponding experimentally measured curves. These model curves are quantitatively about the same, because the right ventricular inflow time constant of the model of Figure 3b is sufficiently small with respect to the nominal cardiac cycle length. However, the model curves become significantly different at higher heart rates, since the time constant is no longer sufficiently small.

## 5. Results

We compute the prediction error of Guyton's graphical analysis as the percentage difference between the average CO and ERAP determined by intersecting the model CO and VR curves (predicted) and the average CO and ERAP measured directly from the intact circulatory model (actual). We compute this prediction error for a wide range of actual, intact circulatory values which is established by varying the baroreflex controllable parameters of the model over their dynamical range [4]. We then report the

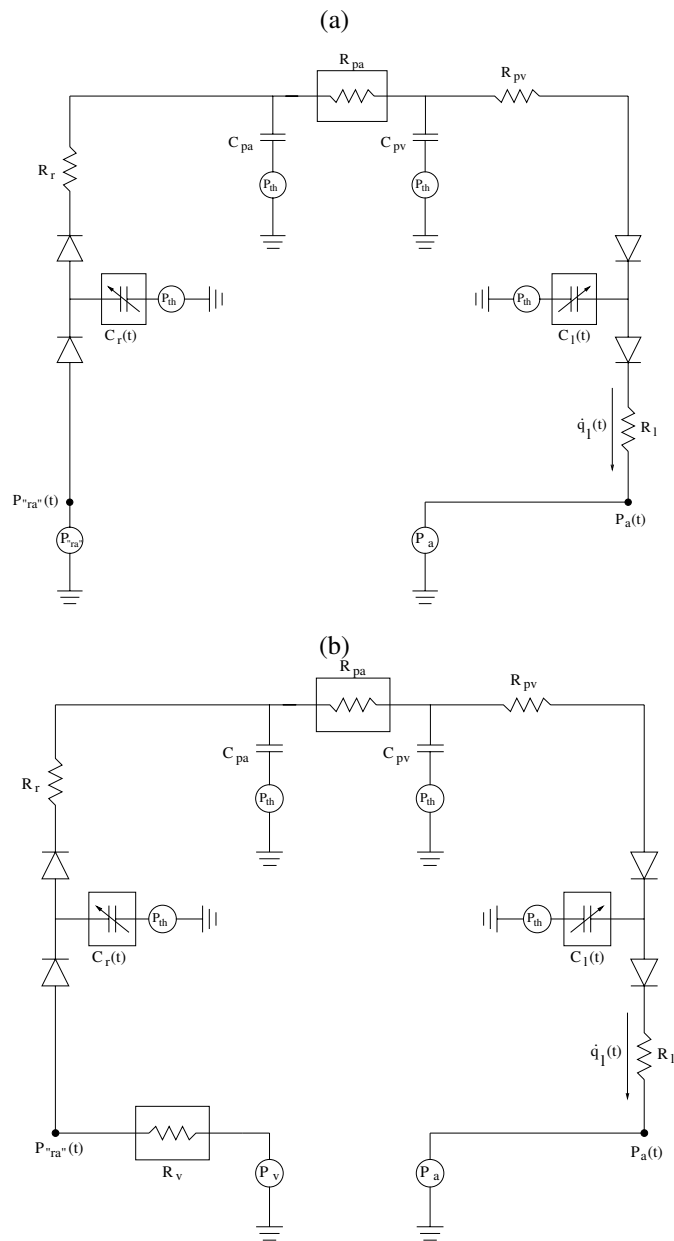


Figure 3. Models for measuring CO curves.

prediction error as a function of actual, average CO and ERAP.

Figure 4 illustrates the prediction errors for Guyton's graphical analysis applied to CO and VR curves measured with constant ERAPs. As expected, this figure demonstrates that the prediction errors are unacceptably high (from ~30-80%) when the average ERAP is near atmospheric pressure and/or the heart rate is high.

Figure 5 shows the prediction errors for Guyton's graphical analysis applied to CO and VR curves measured with pulsatile ERAPs similar to those seen in the intact

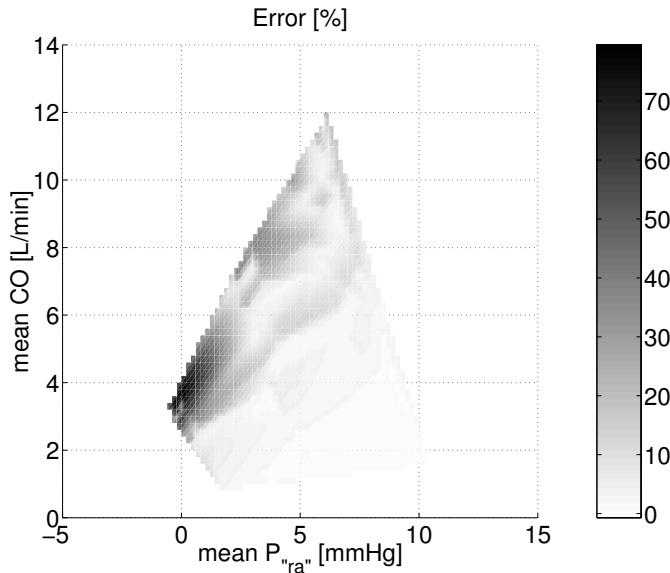


Figure 4. Prediction errors of Guyton's analysis applied to CO and VR curves obtained with Figures 2a and 3a.

circulatory model. The prediction errors here are no greater than  $\sim 15\%$  regardless of the intact circulatory values. As stated above, the model for measuring VR curves in this manner includes a portion of the heart-lung unit (see Figure 2b). Figure 5 was generated with the parameters of this portion of the heart-lung unit adjusted to be identical to the parameters which generated the intact circulatory values. However, we found no statistically significant difference when these parameters were held constant. Thus, the VR curve is essentially independent of the CO curve despite the manner in which the former curve is measured.

## 6. Summary and conclusions

The results of this computational model-based study may be summarized as follows: 1) due to pulsatility and system nonlinearity, the prediction errors of Guyton's graphical analysis can be unacceptably high when the model CO and VR curves are measured by simulating established experimental preparations that apply constant ERAPs; 2) the prediction errors of Guyton's graphical analysis are sufficiently low when the model CO and VR curves are measured by implementing theoretical preparations that apply pulsatile ERAPs similar to those seen in the intact circulatory model; and 3) the model CO and VR curves obtained with the pulsatile ERAPs are practically independent of each other. We therefore conclude that CO and VR curves measured with the established experimental preparations are limited in reflecting intact circulatory behavior. However, Guyton's graphical analysis is, in principle, still valid because of the theoretical possibility

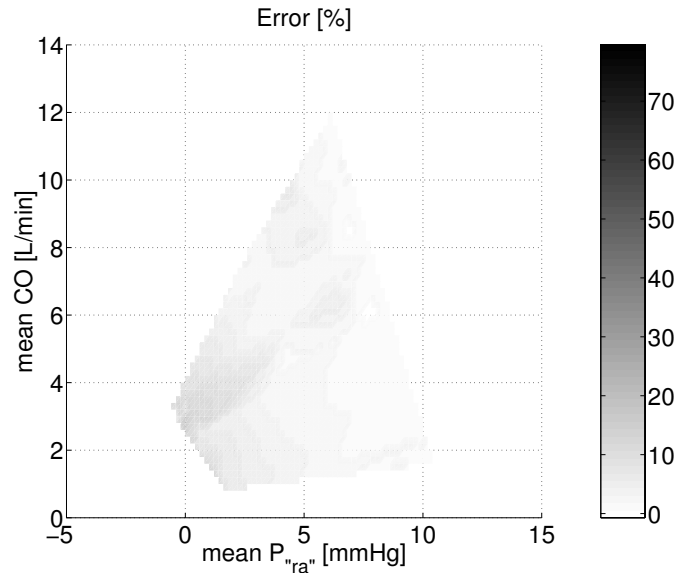


Figure 5. Prediction errors of Guyton's analysis applied to CO and VR curves obtained with Figures 2b and 3b.

of measuring CO and VR curves which accurately reflect intact circulatory behavior and are independent of each other.

## Acknowledgements

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